SAMJ FORUM

ISSUES IN MEDICINE

Surprises of off-label drug use – where had all the Prostin gone?

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The off-label use of drugs is common, particularly in paediatrics, where many drugs have yet to undergo the rigorous scrutiny demanded by authorities such as the Medicines Control Council (MCC) and the US Food and Drug Administration (FDA) before registration.[1,2] Yet some drugs (e.g. paracetamol, salbutamol) are so commonplace in paediatric practice that it may come as a surprise that their use is indeed off-label in many circumstances. Problems may arise when an important drug in everyday (off-label) use is unexpectedly in short supply. An example is dinoprostone, marketed in South Africa as Prostin E2 by Pfizer South Africa (but curiously not listed on their website). Its registered use in South Africa is for induction of labour (as an oral 0.5 mg tablet), yet it is commonly used in South Africa for the emergency maintenance of ductal patency in newborn babies.

Dinoprostone

Dinoprostone is a naturally occurring prostaglandin E_2 that binds and activates the PGE_2 receptor. It is often used as an emergency treatment to maintain the patency of the ductus arteriosus (PDA) in neonates with duct-dependent lesions such as certain forms of cyanotic congenital heart disease (e.g. pulmonary atresia or transposition of the great arteries) and interruption or coarctation of the aorta. The birth incidence of these rapidly life-threatening lesions is 1.0 - 1.8/1 000[3] and administration of dinoprostone is life-saving, 'buying time' for the baby to be transferred to a referral centre for definitive establishment of pulmonary or aortic blood flow by systemic-to-pulmonary shunt or arch repair, respectively. Without maintenance of ductal patency, duct-dependent babies rapidly become critically ill and die.

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Dinoprostone is also used for the longer-term maintenance of ductal patency in low-birth-weight infants with duct-dependent pulmonary circulations but branch pulmonary arteries that are too small for immediate surgical placement of a systemic-to-pulmonary artery shunt.[4]

For these applications, dinoprostone is usually administered as an oral medication. The 0.5 mg tablet is crushed and mixed with water and 0.125 mg aliquots (¼ tablet) are given to the infant by nasogastric tube every 30 - 60 minutes.[4] The side-effects are minimal, but include a small increase in body temperature (generally to less than 37.5°C) and loose stools. This simple method of administration is easily achievable by peripheral hospitals and delivery units, enabling rapid establishment of stable ductal patency before transfer to a tertiary referral centre.

An alternative, intravenous PGE_1 (alprostadil, Prostin VR), requires the placement of secure intravenous access for continuous infusion of alprostadil and close monitoring of respiratory effort. Intravenous PGE_1 frequently causes apnoea requiring intubation and ventilation for safe transfer. Peripheral hospitals and delivery units are often not capable of such interventions and do not stock intravenous PGE_1. There are no alternatives to maintain ductal patency.

The whistle-blower case

In January 2009 we received a call from a paediatrician at a regional hospital. A small infant with pulmonary atresia, dependent on a PDA for flow to his pulmonary arteries, required time to grow to sufficient size to enable the placement of a modified Blalock-Taussig shunt. After assessment at Red Cross War Memorial Children's Hospital he had been returned to the regional hospital for growth, receiving a quarter Prostin E2 tablet half-hourly for maintenance of his PDA. The hospital was about to run out of Prostin E2 and was unable to replenish the supply from local clinics or hospitals, since these had all also run out. No stocks were available from local suppliers. The baby was transferred back to Red Cross Hospital on intravenous alprostadil, and required early placement of a systemic-to-pulmonary artery shunt. The procedure was complicated by early shunt stenosis and re-operation was required for shunt revision, which could have been avoided had he been allowed to grow until the vessels were larger, lessening the risk of shunt thrombosis.

Where had all the Prostin gone?

Unbeknown to South African paediatric cardiologists and most pharmacists nationally, stocks of Prostin E2 had become critically depleted. Pfizer is said to have redesigned the packaging of Prostin E2, and stocks became depleted while awaiting re-registration with the Medicines Control Council.

Why did Pfizer fail to inform paediatric cardiologists and pharmacists of an imminent and foreseeable shortage? Apparently Pfizer representatives had informed obstetric/gynaecological practitioners, but according to their spokesperson they were 'not allowed' to discuss an off-label drug with paediatric cardiologists, despite the fact that Prostin E2 is the only oral dinoprostone available in South Africa and has been in use as outlined for many years. A rapid survey of all paediatric cardiac referral centres in South Africa revealed that this was a national problem in both the public and private health sectors. At the same time, Pfizer could not tell us with certainty when supplies would be resumed.

To their credit, when the potential impending crisis in congenital cardiac care was brought to Pfizer's attention in mid-January 2009, they expedited the delivery of fresh stocks to suppliers, and by Monday 26 January the supply of Prostin E2 had resumed nationwide. Pfizer assured us that there was sufficient stock 'for two years' and that future supplies would be 'uninterrupted', but unfortunately were not prepared to give these assurances in writing.

So ended a brief yet worrying period during which we could not ensure the safe transfer of neonates with duct-dependent congenital cardiac lesions and were having to start making difficult management decisions with regard to timing of their cardiac surgery. Nevertheless, it remains of concern that the supply of essential and life-saving drugs can be prone to sudden, unexpected interruptions; and perhaps more so that producers consider themselves legally constrained from disclosing imminent foreseeable drug supply interruptions if such drugs are used off-label. The reluctance of pharmaceutical companies to discuss issues pertinent to the use of off-label drugs – even urgent issues such as notification of interruption of supply – is grounds for much concern. It surprises us that medical practitioners working for this company are not prepared to inform colleagues – even 'off the record' – considering that Prostin is listed for paediatric use in the latest version of the essential drugs list for South Africa.[5]

The FDA becomes permissive

In the USA, the FDA's prohibition on pharmaceutical companies to inform medical practitioners of important changes in indications for off-label drugs has been judged in the US District Court of Columbia as unconstitutional, and the FDA's restrictive stance vigorously criticised. The judgment included the statement: 'In sum, the court finds that the restrictions in the Guidance Documents [of the FDA] are more extensive than necessary to serve the asserted government interest and that they unduly burden important speech.'[6] In essence, the district court therefore had found that the FDA had violated the First Amendment of the US Constitution. On appeal, the US Court of Appeals for the District of Columbia dismissed the finding of the district court pertaining to the unconstitutionality of the FDA's prohibitions on procedural grounds, since it 'was not ripe for decision', but noted that it 'certainly did not criticize the reasoning or conclusions of the district court'.[7]

Thereafter, the FDA reconsidered its role in the regulation of off-label drug use, suggesting 'a more permissive attitude toward the promotion of off-label uses of drugs'.[8] In its recently published 'Guidance for Industry' document[9] the FDA recognises 'that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products'.

Conclusion

While US law is not necessarily applicable in South Africa, surely common sense demands that in the interests of public health, information of a life-threatening shortage of any drug,

Pfizer responds

Pfizer South Africa welcome this article, which seeks to inform and protect the interests of both patients and physicians, and thank *SAMJ* for the opportunity to clarify some of the points made for the benefit of readers.

Product shortages do occur from time to time for a variety of reasons. In the case of Prostin E2 we found ourselves in an unfortunate situation whereby our third-party supplier ran out of stock. This was totally unexpected and, because they are a third-party supplier, resulted in our having to follow a number of different logistical as well as regulatory processes.

Keeping patients and physicians informed and protecting their interests is of paramount importance to Pfizer South Africa, and we greatly appreciate feedback. We will incorporate De Decker *et al*.'s suggestions in our communications to ensure that all relevant health care professionals are promptly informed of such issues within the confines of the industry regulations, and assure readers of our commitment to providing uninterrupted access to our medicines for patients and physicians.

Brian Daniel
CEO and Country Manager
Pfizer South Africa

even in off-label use, should be disseminated as widely as possible to relevant health professionals. This would allow clinicians and pharmacists to implement contingency plans and/or changes in management strategies in order to minimise potential loss of life or increased morbidity resulting from the shortage of the drug.

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PERSONAL VIEW

Santa Claus or grandfather clause?

Dear Aunt Ethel,

During the second six months of internship at Groote Schuur Hospital, when we were covering four internal medicine wards divided between two firms, Toby called an informal meeting.

'Look, I'm the only Jewish house officer among the six of us: Christmas means nothing to me. I'll be on duty all day provided that I'm off for the Jewish holidays.'

This was a fair offer, so Toby duly celebrated his religious holidays free from any ward work or calls. The rest of us looked forward to a guaranteed Christmas off duty: festivities looked very promising as nurses and doctors were arranging an all-day party. However, a complication was brewing. Toby had become interested in a nurse who was a gentile – and an organiser of the Christmas entertainment. As this involvement progressed he sounded less and less convinced that Christmas meant nothing to him, and discussed mistletoe and mince-pies in longing terms. There was also the matter of who might

From photograph of the first resident medical staff at Groote Schuur Hospital, February - July 1938. Dr R A (Paddy) Caldwell is on the right.

distract the lovely young lady in question during the festivities if he was slaving away all day on the ward. Eventually he put his cards on the table, choosing a good psychological moment: a seventh intern had been seconded to our wards.

'Look, Christmas now means more to me than I suspect it does to the majority of you. How about splitting the duties that day? Draw names out of a hat. 6 am to 6 am, four-hour shifts between six house-officers, the seventh has the day off.'

This was reasonable: personal conquests were non-existent; we liked Toby; we wanted his romance to succeed. In any case only four hours each, with an outside chance of none at all, seemed hardly a problem. *Chutzpah* baffles logic. Then the draw took place. Fair and square, Toby pulled the seventh

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straw, and three of us landed prime time shifts. Mine was from 2 pm to 6 pm.

Christmas was bedlam. After a quick ward round, I acted as Santa Claus to the four wards: only the most confused patient recognised her doctor. A patient with meningitis whom we had regretted resuscitating after he arrested proved not to be brain-dead: just stone-deaf. He roared with laughter at the little elasticised animal which Santa, on a whim, produced. Then I tore off to a farm an hour's drive away to be Father Christmas again, on a blazing-hot day, wearing a mask that denied visual acuity, mounted side-saddle on a recalcitrant horse. I bolted an enormous roast-turkey dinner and screamed back into Cape Town in time for my shift. Things were hotting up on the wards after a peaceful morning. Admission after admission rolled in, preventing any easy departure at 6 pm: more like 8.30. By then the all-day festivities were at an end.

Toby had had a great day and on the ward next morning, he asked how our Christmas had been. I recall a sardonic and laconic: 'Nowell? Ja … Fine!'

He did have the decency to marry her.

I have been Father Christmas on many Yuletide occasions since, riding pillion on a motor-bike once, arriving in a speed-boat on another stint. One did not really question why one went beyond the call of duty. Now at last I know the reason for the compulsion: it's inborn, it's genetic …

When I e-mailed Kit Vaughan to congratulate him on his biography of Allan Cormack, *Imagining the Elephant*, he told me about *At the Heart of Healing*, the recently published history of Groote Schuur Hospital's first 70 years. With a holiday ahead, I bought a copy. Simultaneously my wife got a call from Jenny Still, a journalist and family friend in Cape Town. At a UCT summer-school lecture she'd seen a DVD of Dr Caldwell as Santa Claus at Groote Schuur Hospital.

It was in 1937, so it was not I: and it was New Somerset Hospital, not Groote Schuur: the former was closing as the latter was due to open. My father, as a 'June bride', had walked into history by being on the last resident staff of Somerset and the first of Groote Schuur: but I did not know about any Santa activities.

A night or two later I received a phone call from Howard Phillips, a professor in the Department of Historical Studies at UCT and one of the chief authors of the book. Jenny Still had spoken to him after the lecture. He suspected that Santa Claus was my late father, and if so would I be interested in seeing some film footage? Since the upcoming holiday was in the Cape, I accepted with alacrity and met him a fortnight later in the UCT history building, where he showed me a DVD made from film footage taken by a nursing sister. This documented the transition from New Somerset Hospital to Groote Schuur as 1937 ended and 1938 began.

Although Father Christmas jumped around in a manner not reminiscent of my Dad, the jerky actions matched those of which his grandchildren complain regarding their father. When the unmasking came, there was *my* father, just as he looked in the photograph I have in my office: of the first resident staff of GSH. Our sons have an inherited white-bearded task ahead of them; and the book is well worth reading.

Yours affectionately

Robert-Ian